DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

M2312N

19900 MacArthur Blvd., Ste 300
Irvine, California 92612-2445
Telephone (949) 798-7600

WARNING LETTER

January 11, 1999 WL-22-9

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Allen Y. Chao, President and CEO
Watson Laboratories, Inc.
311 Bonnie Circle
Corona, California 91720

Dear Dr. Chao:

During an inspection of your Corona, California drug manufacturing firm conducted between December 7 and December 18, 1998, our investigators documented serious deviations from the Current Good Manufacturing Practice Regulations (Title 21, Code of Federal Regulations, parts 210 & 211). These deviations cause your drug products to be adulterated within the meaning of Section 501 (a) (2) (B) of the Federal Food, Drug, and Cosmetic Act. For example:

1. Failure to assure batch uniformity and product integrity by establishing and following written procedures that describe the in-process controls, tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of these manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the product. [21 CFR 211.110 (a)].

   Specifically, your firm failed to properly validate the manufacturing processes used in Butalbital, Acetaminophen, and Caffeine tablets (50/500/40 mg), Hydrocodone/APAP tablets, and Diltiazem Extended Release (Dilacor) Capsules. Although process validation was performed for these products, the protocols failed to include:

- Validation lots consisting of three, consecutive, successful lots; and/or

- Validated and consistent sampling techniques or procedures when collecting granulation samples for blend uniformity testing; and/or

- Adequate procedures for evaluating failed blend uniformity testing of samples collected from blenders or drums; and/or

- Specifications for in-process samples were not established prior to validation lots being manufactured.

2. Failure to review and approve batch production and control records to determine compliance with all established, approved procedures before a batch is released or distributed. Any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and follow-up. [21 CFR 211.192]

   Specifically, your firm failed to perform adequate investigations into product failures and deviations. Foreign material found in one of five drums of Hydrocodone / APAP (10/325 mg), Lot #53904B98 was simply removed from the top of the granulation. The majority of the drum's remaining granulation was made into tablets, which were later approved and released. The particles were not identified, and a thorough investigation was not conducted to determine the possible source and extent of the contamination.

Your investigation into black specks or particles in Dilacor lot #DB003M98 was also inadequate. The investigation summary states that the particles were most likely from the ethyl alcohol used as the granulation wetting solution. However, the report from [redacted] who identified the particles isolated from the tablets and the alcohol, clearly states that none of the particles found in the alcohol were found in the tablets or granulating solution.

Your firm's investigations into multiple, out-of-specification blend uniformity test results consistently fail to identify the cause of the test failure, fail to determine whether the granulation blend is truly uniform, and fail to solve the problem to potentially improve blend uniformity. Virtually all blend uniformity failures are attributed to poor sampling technique since the active ingredient is "finer" in particle

size than the other materials in the granulation. This explanation is used when the sample tests super-potent or sub-potent. [redacted]

3. Failure to maintain laboratory records to include complete data derived from all tests necessary to assure compliance with established specifications and standards. [211.194] Specifically, your firm failed to control raw laboratory data, in that an "unofficial" or "personal" notebook was used by at least one analyst to record method and testing data. For example, the data in one analyst's "personal" notebook differed from that recorded in the "official" laboratory notebook.

4. Failure to establish sufficient laboratory controls to assure that components, in-process materials and drug products conform to appropriate standards of identity, strength, quality and purity [21 CFR 211.160]. Specifically, review and use of HPLC chromatograms failed to find inaccuracies and inconsistencies in the data.

We are concerned that the observations and cites listed above are similar to cites noted in a previous Warning Letter sent to your firm on January 27, 1998, as well as previous FD-483 observations. A meeting between your company and FDA district management is scheduled for January 15, 1999. Please come prepared to discuss your firm's approach to process validation, blend uniformity testing and test failures, method validation, and your approach to making corrective actions.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. A list of observations (FDA 483) was issued and discussed with you at the conclusion of the inspection. It is your responsibility to assure adherence with each requirement of the Good Manufacturing Practice regulation and other applicable regulations. Federal agencies are advised of the issuance of all warning letters about drugs and devices so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to do so may result in regulatory action without further notice, including seizure and/or injunction. You should notify this office in writing, within fifteen (15) working days of receipt of this letter, of the specific steps you have taken to correct the noted violation, including an explanation of each step taken to prevent the recurrence of similar violations. If corrective action

cannot be completed within fifteen (15) working days, state the reason for the delay and time within which the corrections will be completed. Your reply should be addressed to:

Dannie E. Rowland, Compliance Officer
U.S. Food and Drug Administration
19900 MacArthur Blvd., Ste. 300
Irvine, CA 92612

Sincerely,

Elaine C. Messa
District Director

cc: State Department of Public Health
Environmental Health Service
Attn: Chief Food and Drug Branch
601 North 7th Street MS-357
P.O. Box 942732
Sacramento, Ca 94234